REMARKS

Entry of this amendment is respectfully requested. No new matter is added by the amendment, as the amended claims are fully supported by the application as filed (for example, implantability is disclosed at the first full paragraph of page 12, the types of polymers are disclosed at the first full paragraph of page 11, and the combination of an oxidizing agent and a reducing agent is found in claim 63; the deletion of gloves from claims 92-94 reflects that they, unlike the other devices recited in those claims, are not implantable; and the added claims 99-111 are supported by the previously filed claims, adding a family of claims dependent on claim 76). A version of the amended claims showing the changes made from the application as it existed prior to this amendment is attached.

Claims 61-111 are in this application, claim 63 having been canceled, claims 61, 64, 65, 68, and 92-94 having been amended, and claims 99-111 having been added by this response. Claims 61-69, 73, 76, 92, 93, 95 and 96 were under examination, and were rejected under 35 USC 102(b) and/or 35 USC 103(a). These rejections are respectfully traversed in view of the amendment.

The restriction requirement

In the response to the restriction requirement, filed February 19, 2002, Applicants elected for examination the species where the oxidant is elemental iodine, the oxidant-producing component is a reducing agent that is an alkali iodide salt and an oxidizing agent that is an alkali iodate salt, the proton donor is glucose oxidase, the polymer is a hydrophobic polymer that is a silicone polymer and the medical device is an implant; and identified claims 61-69, 73, 76, 92, 93, 95, and 96 as reading on the elected invention.

Applicants' attorney notes that claims 74 and 75, both of which depend from claim 73, also read on the elected species. The error in identification of the elected claims is regretted, and it is respectfully requested that claims 74 and 75 be examined with those claims previously elected.

Claims 99-111 have been added dependent directly or indirectly on claim 76. Of these added claims, claims 99-104 and 109-111 read on the elected invention, so that, with the change noted above, the claims under examination would be claims 61, 62, 64-69, 73-76, 92, 93, 95, 96, 99-104, and 109-111.

The 35 USC 102(b) rejection

Claims 61-63, 65, 66, 68, 69, and 92-93 were rejected under 35 USC 102(b) as being anticipated by Karns, US Patent No. 1,867,222. This rejection, as applied to the amended and added claims, is respectfully traversed.

The invention

The invention of the present application, as defined by the broadest claim 61, is an implantable anti-infective medical device, comprising a polymeric matrix selected from the group consisting of thermoplastic polymers, thermosetting polymers, and hydrogels, containing within the matrix an oxidant-producing component comprising a reducing agent and an oxidizing agent that, when wetted, causes the formation of an oxidant and sustained release of the thus-formed oxidant into and about the polymeric matrix so that the matrix serves as an anti-infective reservoir.

Elected dependent claims specify the oxidant, the oxidant-producing component, the presence of a proton donor and its nature, the nature of the device, and the like.

The invention is particularly advantageous as it provides implantable medical devices having anti-infective activity which are energizable generally simply by implantation and provide sustained

release of an anti-infective oxidant so that the device serves as an anti-infective reservoir, helping to prevent the infections commonly associated with implantable medical devices.

Karns

Karns discloses a surgical dressing that will release iodine on application to a moist wound or upon being moistened by water. The dressing comprises a web of surgical gauze or the like impregnated in part of its extent with iodine-containing material (such as an iodide or an iodate or periodate) and impregnated in another part with an iodine-releasing material (such as an oxidizing agent and an acid if the iodine-containing material is an iodide, or a reducing agent if the iodine-containing material is an iodate or periodate). The web is impregnated partwise with the solutions of the two materials, dried, and then folded so that the areas overlie one another.

Discussion

Karns fails to anticipate any of claims 61-63, 65, 66, 68, 69, and 92-93 as amended because these claims all require that the device be an implantable device, made from a thermoplastic, thermosetting, or hydrogel polymer, and the dressing of Karns is not implantable — it is a dressing for external application — and it is not made of a thermoplastic, thermosetting, or hydrogel polymer — it is disclosed as being of surgical gauze (i.e. cotton). Applicants note that claim 76 was not subject to this rejection and that added claims 99-105 and 110-112 are therefore also free of this rejection since they depend directly or indirectly from claim 76.

Accordingly, Karns does not anticipate claims 61-63, 65, 66, 68, 69, and 92-93 as amended of claims 99-105 and 110-112 as added, and withdrawal of the rejection is requested.

The 35 USC 103(a) rejection

Claims 61-69, 73, 76, 92, 93, 95, and 96 were rejected under 35 USC 103(a) as being unpatentable over Montgomery et al., US Patent No. 4,576,817, in view of Karns and Zanowiak, "Pharmaceuticals". This rejection, as applied to the amended and added claims, is respectfully traversed.

The invention

The invention of the present application has been discussed above with respect to the rejection under 35 USC 102(b).

Montgomery et al.

Montgomery et al. discloses enzymatic absorbent materials such as bandages and pads for body contact applications containing a serum-activated oxidoreductase enzyme (such as glucose oxidase). The enzymatic material may also contain a peroxidase enzyme and an oxidizable substrate (such as a substrate specific to the oxidoreductase enzyme and a thiocyanate, chloride, or iodide salt). The enzymatic absorbent materials may be prepared from standard absorbent precursors (such as woven fibers, porous foam pads, absorbent membranes, and solvent-based porous elastomers, gauze bandaging, etc.) or the enzyme may be incorporated into absorbent fibers and these fibers converted into bandages or pads.

Montgomery et al. does not disclose the use of an oxidizing agent such as iodate, or the use of iodate as an iodine source. The Examiner states that "Montgomery does not disclose using an iodide", but this is incorrect - while claim 13 uses "iodine", it is an evident error for "iodide" mentioned at column 4, the paragraph at lines 6-13.

Further, the Examiner notes that Montgomery states that a contraceptive flexible foam pad can be obtained "by incorporating spermicidal composition in the invention". The clear implication from

this is that the formulation of Montgomery et al. as described (i.e. containing the oxidoreductase enzyme and optionally the peroxidase enzyme and oxidizable substrate) is not in itself spermicidal.

Karns

Karns has been discussed earlier with respect to the rejection under 35 USC 102(b).

Zanowiak

Zanowiak discloses generally the formulation of pharmaceuticals, and discloses in particular that a controlled-release implantable contraceptive formulation comprises closed silicone (dimethylsiloxane-methylvinylsiloxane copolymer) capsules containing levonorgestrel.

Zanowiak offers neither disclosure nor suggestion of the use of silicones as a base material containing within the silicone matrix a pharmaceutically active agent; and offers neither disclosure nor suggestion of implantable anti-infective medical devices containing an oxidant-producing component (and, *a fortiori*, neither disclosure nor suggestion of the specific oxidant-producing components presently claimed).

Discussion

The Examiner reasons that "Motivation to utilize the teaching of Karns, notably a material comprised of an iodate and iodide that, upon activation with fluid or water, releases iodine, would have arisen in order to obtain the full antiseptic effect of the iodine (which is shown to be useful and desired in the invention of Montgomery. As siloxane polymers are known to be used for contraceptive therapy, one with ordinary skill in the art would have known to use such material to deliver the invention of Montgomery, i.e. a contraceptive flexible foam." Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991), cited in MPEP 2142.

First, Montgomery et al. does not teach or suggest an implantable anti-infective medical device, comprising a polymeric matrix selected from the group consisting of thermoplastic polymers, thermosetting polymers, and hydrogels, containing within the matrix an oxidant-producing component comprising a reducing agent and an oxidizing agent that, when wetted, causes the formation of an oxidant and sustained release of the thus-formed oxidant into and about the polymeric matrix so that the matrix serves as an anti-infective reservoir. Although Montgomery does disclose the apparent incorporation of an enzyme into a fiber and a foam (Examples II and III), Applicants note that in Example II, the enzyme was found in the aqueous component of an emulsion and not in the fiber forming organic component; and in Example III, the enzyme was also found in a dispersion. Further, these examples contain only an enzyme and do not contain a reducing agent and an oxidizing agent. The other examples disclose only deposition onto spun cotton pads, and not incorporation into the polymeric matrix.

This deficiency of Montgomery et al. is not remedied by Karns, which discloses only the absorption of active ingredients onto surgical dressings (cotton gauze and the like), and does not disclose implantable devices, as discussed earlier. Moreover, the Examiner's statements not to the contrary, there is no motivation in either Montgomery et al. or in Karns to put the iodide/iodate system

of Karns into the enzymatic system of Montgomery et al. because the essence of Montgomery et al., like that of the present invention, is to have a system in which the active ingredients of the system are added simultaneously and are all present in the polymeric matrix, and the iodide/iodate system of Karns et al. cannot be used for absorption onto the cotton gauze and like materials of Karns in this way because dissolution of the necessary components would result in the formation of iodine in the impregnation solution and failure of the process.

The Examiner cites Zanowiak only for the use of silicone in the contraceptive devices, and the deficiencies of Zanowiak as a reference have been pointed out already: it shows the use of silicone as a "container" for a levonorgestrel pellet, and does not show the presence of active ingredients in a polymeric matrix, nor specifically of oxidant-producing compositions. Thus the combination with Zanowiak proposed by the Examiner (a) is improper because there is no motivation for the combination in any of the references, Zanowiak is directed to such different technology than Montgomery et al. and Karns that a person of ordinary skill in the art looking to amend either would not look to a reference that discloses Norplant™; and (b) in fact adds nothing to the proposed combination of Montgomery et al. and Karns because it does not suggest the use of silicones as a matrix material but rather as a "container" for the levonorgestrel.

With respect to claim 64, there is no disclosure or suggestion of solid particles dispersed within the matrix: both Montgomery et al. and Karns refer to the use of solutions.

With respect to claim 76 and its dependent claims, there is no disclosure or suggestion that the polymeric matrix should be a hydrophobic polymer.

Regarding rejection of the anti-infective claims, although Montgomery et al. teaches a "...suitable oxidoreductase enzyme is glucose oxidase ..." and that "...the material can also contain iodine along with the enzyme..." as stated by the Examiner, Montgomery et al. teaches iodine generating activity aimed at treating wounds in which serum, and thus glucose, is present through application of "Enzymatic absorbent materials such as bandages and pads, for body contact applications ...upon contact of the enzymatic materials with serum..." (Abstract, see also claims 1 and 20). Montgomery et al. does not teach how glucose oxidase and iodide could be incorporated into man-made nonabsorbent synthetic polymers used to fabricate implantable medical devices. On the contrary, Montgomery makes clear that their anti-infective formulations require absorbent material (claims 1 and 20), thereby teaching away from art concerned with nonabsorbent polymeric materials addressed in these claims.

In particular, whereas the present patent filing teaches art for introducing iodine-generating chemistry through the use of dry chemical formulations co-mixed into man-made synthetic polymers used in the fabrication of implantable medical devices, the art taught by Montgomery et al. teaches the use of liquid chemical formulations for incorporation into absorbent materials. Those knowledgeable in the art are aware however that it is not feasible to include moisture in the base materials of thermoplastic and condensation polymers such as polyurethanes and polysiloxanes during extrusion and molding of medical devices because water has a highly deleterious effect on the final product. It is thus known that thermoplastic polyurethanes, for example, must be thoroughly heated and dried for several hours before the raw material can be properly melted, molded and extruded into a device. The polymerization of diisocyanate monomers with diols to produce elastomeric polyurethanes used for fabrication of medical devices likewise is adversely affected by the presence of water because water will degrade isocyanate and therefore interfere with successful polymerization and fabrication of the final product.

Furthermore, the high temperatures used in extrusion and molding of polyurethanes and polysiloxanes (>150 °C), and other thermoplastic polymers common to medical devices, negates any

possibility of using the art specifically taught by Montgomery et al.. This is obvious to those of ordinary skill in the art because it is known that aqueous enzyme solutions are heat labile and not tolerant to the temperatures required for extrusion and molding of many medical devices. Nor would Montgomery et al.'s enzyme formulations tolerate the high temperatures typically encountered during sterilization of medical devices which likewise would cause denaturization of their enzyme formulations rendering the devices devoid of any possibility of expressing anti-infective activities when implanted in the body.

Accordingly, Montgomery et al in view of Karns and Zanowiak do not make claims 61, 62, 64-69, 73, 76, 92, 93, 95, and 96 as amended and claims 99-104 and 109-111 as added unpatentable, and withdrawal of the rejection is requested.

Conclusion

For the reasons given above, Applicants submit that claims 61, 62, 64-69, 73, 76, 92, 93, 95, and 96 as amended and claims 99-104 and 109-111 as added are not anticipated by Karns nor unpatentable over Montgomery et al in view of Karns and Zanowiak. Entry of the amendment, and re-examination and allowance of the claims are respectfully requested.

Respectfully submitted,

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Amended text showing amendments made
(additions in bold, deletions struck through)

Claims 61, 64, 65, 68, and 92-94:

61. (Amended) An **implantable** anti-infective medical device, comprising a polymeric matrix **selected from the group consisting of thermoplastic polymers, thermosetting polymers, and hydrogels,** containing within the matrix an oxidant-producing component **comprising a reducing agent and an oxidizing agent** that, when wetted, causes the formation of an oxidant and sustained release of the thus-formed oxidant into and about the polymeric matrix so that the matrix serves as an anti-infective reservoir.

64. (Amended) The anti-infective medical device of claim **61** ~~63~~ where the oxidant-producing component further comprises a proton donor that, in combination with the reducing agent and the oxidizing agent, forms solid particles dispersed within the polymeric matrix in sufficient amount to provide anti-infective activity to the medical device.

65. (Amended) The anti-infective medical device of claim **61** ~~63~~ where the reducing agent is a water soluble iodide salt.

68. (Amended) The anti-infective medical device of claim **61** ~~63~~ where the oxidizing agent is selected from the group consisting of anhydrous alkali iodine oxide salts, iodine pentoxide, inorganic and organic peracids, oxidase enzymes, and combinations thereof.

92. (Amended) The anti-infective medical device of claim 61 that is selected from the group consisting of catheters, guidewires, ~~gloves,~~ prostheses, implants, and contraceptive devices.

93. (Amended) The anti-infective medical device of claim 76 that is selected from the group consisting of catheters, guidewires, ~~gloves,~~ prostheses, implants, and contraceptive devices.

94. (Amended) The anti-infective medical device of claim 77 that is selected from the group consisting of catheters, guidewires, ~~gloves,~~ prostheses, implants, and contraceptive devices.